

REMARKS

Amendments to the claims have been made to respond to the issues and concerns raised in the Office Action, to clarify aspects in the specification and claims, and to refine claim language. The amendments are believed to be consistent with the disclosure originally filed. The amendments also have been particularly presented to avoid, where applicable, any admission or estoppel, generally, negatively affecting the scope of protection provided by the disclosure and claims of the present application, and also in a manner that avoids prosecution history estoppel, limitation of the scope of equivalences, or the like. The Applicant amends claims 1, 16, 25, 167, 172, and 174-183. Claims 2-4, 13-15, 18, 30-164, 168, 171, and 184 have been cancelled. Claim 185 has been added. Thus, claims 1, 5-12, 16-17, 19-29, 165-167, 169-170, 172-183, and 185 remain in this application and are believed in a condition for allowance.

As a preliminary matter, the Applicant notes that many of the issues and concerns related to the present case present complex and intertwining considerations. Accordingly, in the event questions remain, the Applicant requests the opportunity to pursue an interview to resolve any issues or concerns.

The Office Action expressed certain nonstatutory double patenting concerns. While the Applicant disagrees that the pending claims raise a double patenting issue, the Applicant notes that it is willing to execute a terminal disclaimer so as to expedite prosecution of the current case and anticipates discussing the details regarding the same by way of an interview.

The Office Action raised obviousness and novelty concerns with respect to the Seidel (1997) reference. The Applicant disagrees with the concerns raised. Moreover, the Applicant notes that Seidel is both an inventor in the current case and a co-author of the reference. Unless a reference is a statutory bar, it may be removed and the rejection may be overcome by a showing that the reference was published by the Applicant himself. MPEP § 715.01(c); In re Facius, 408 F.2d 1396 (CCPA 1969). As a further

showing, the Applicant submits as Exhibit A to these Remarks a copy of the Affidavit of co-inventor George Seidel under 37 C.F.R. § 1.132, submitted in a parallel filed patent application. The Applicant believes that this document or a similar document referring to the instant application and the specific claims should be sufficient to remove Seidel (1997) as a reference. Because the reference must be removed, it cannot be cited for any novelty issues. Further, combinations of references including Seidel (1997) do not establish a prima facie case of obviousness because Seidel (1997) must be removed and the remaining combinations of references do not disclose all the elements of the claimed invention as required by MPEP § 2143 and In re Royka, 490 F.2d 981 (CCPA 1974).

The Office Action raised various obviousness concerns with respect to claims 5, 7, 9, 11-12, 18-22, 29, and 165-168. The Applicant disagrees with these concerns. Moreover, the Applicant notes that these are dependent claims and are allowable for the reasons discussed in these Remarks with respect to the independent claims.

The Office Action raised obviousness concerns with respect to claims 178-180 citing Seidel (1996) and Rens. The Applicant disagrees with these concerns. First, the Applicant notes that the sample rate discussed by Rens is not the same as the sort rate claimed by the Applicant. A sample rate refers merely to the number of fluorescent events analyzed each second, whereas a sort rate refers to the actual number of sperm sorted each second. There are less sperm sorted each second than are analyzed because not every analysis event yields a conclusion certain enough to warrant a sort. As stated in Rens at column 4, line 17, "the elliptical nozzle of this invention is capable of orienting in excess of 60% of sperm for sorting." This means that only about 60% of the sperm sampled in Rens are actually sorted. As further discussed in Rens at column 2, lines 4-10, as many as 60%-80% of sampled sperm detected by other processes are not sorted. Consequently, regardless of the sample rate values discussed by Rens, at best only about 60% of the number of sampled sperm are actually sorted. Further, this 60% value is a best-case figure, and Rens does not discuss for which particular sample rate the 60% value was achieved nor the parameters required to achieve the same. In fact, Rens does

not discuss any actual sort rates achieved at all. Accordingly, Rens cannot support an obviousness concern with respect to the sorting rates recited in the Applicant's claims.

Second, the Office Action cites Rens at column 3 as supporting an obviousness concern raised with respect to the collection containers of the Applicant's claims. However, the cited teaching of Rens relates only to the dimensions of a nozzle in order to properly orient sperm. This is significantly different from the Applicant's claims, which recite the dimensions of a collection container in order to reduce damage to sperm cells. Accordingly, the current case identifies an entirely different problem than that of Rens and solves it in an entirely different manner than that of Rens. Moreover, merely because the solution to a substantial problem appears simple in hindsight does not make it obvious, as suggested by the Office Action. The current case discloses solutions to the problems associated with the collection of delicate, non-repairing cells. The description sets out the problem:

"[I]t has always been known that the sperm themselves are extremely delicate cells. While this factor at first glance seems like it might be considered easily understood, in fact, the full extent of the cells' sensitivities have not yet been fully explored. In the context of flow cytometry in general, most sorted cells or particles have often been spherical or otherwise physically able to withstand a variety of abuses. This is not the case for sperm cells." Specification at page 3, lines 19-24.

* * *

"In one regard this may be due to the fact that sperm cells are in a class of cells which are non-repairing cells. That is, they do not have the ability to repair themselves and hence, they may need to be treated much more sensitively than is typical for flow cytometers or other handling equipment." Specification at page 15, lines 3-7.

The current case teaches the discovery that a significant source of damage to sperm cells is by impact with the collection container into which they are collected and sets forth a solution:

"[W]hen the cytometer source establishes cells which are physically delicate cells as the cells to be sorted, it may be important to provide some type of cushioning element such as a wide collection tube for which the opening width (18) serves to position the walls of the container in a manner which avoids contact with the cells. Thus the tube does not present side walls so close that there is any significant probability of contact between those cells being sorted and the walls of the tube. In this manner, in addition to the collector fluid (17), it may be desirable to include a wide collection tube as well. Perhaps merely providing a wide opening to the container which serves as part of the collector

(14) may be sufficient. For applications utilizing high speed sorting of sperm cells, it has been found that providing a container having an inner diameter opening of at least 15 millimeters is believed to be sufficient. Specifically when utilizing a 14 ml Falcon test tube in such an application, minimal physical damage to the cells as a result of the collector (14) has been discovered.

It should be noted that even the 14 ml Falcon test tube may not be optimum. Specifically, it is believed that designing a collection container which matches the geometry of the stream (that is, a "stream-matched container") may be most optimal. This stream-matched container may have any or all of the following characteristics: a relatively wide orifice, an elliptically shaped orifice, a lesser height to width ratio than currently involved, an angled or otherwise coordinated presentation such as may present side walls which are parallel to the falling streams, and the like." Specification at page 15, lines 24-28, and page 16, lines 1-15.

Because Rens does not disclose the problem of sperm cells being damaged by contact with the collection container, one skilled in the art could not rely on the teachings of Rens to develop a solution thereto. Accordingly, Rens cannot support an obviousness concern raised against the collection containers of the Applicant's claims.

The Office Action raised novelty concerns with respect to claims 1-2, 6, 8, 10, 16-17, 25, 28, 169-176, and 181-184, citing Seidel (1996). The Applicant disagrees with the concerns raised. However, in order to facilitate examination of the current case, the Applicant has amended claims 1, 174-176, and 181-183 to recite "a rate of at least 1200 sorts per second". The Applicant notes that this sort rate does not appear in Seidel (1996), and a novelty concern has not been raised to this recitation with respect to the Seidel (1996) reference. Accordingly, the Applicant believes the novelty concern with respect to Seidel (1996) has been fully addressed.

The Office Action raises a number of indefiniteness concerns. Regarding the recitation of "a low number of separated non-human sperm," the Applicant disagrees with the indefiniteness concern raised. However, to facilitate examination of the current case, the Applicant has amended claims 1, 174-180, and 182-183 to recite "having a number of separated sperm cells less than about one-half the number of sperm cells of said typical insemination dosage." The Applicant notes that the number of sperm cells in a typical insemination dosage is well within the ordinary skill in the art for common agricultural livestock animals. In bovine applications, for example, as discussed in the

specification at page 19, lines 12-14, an absolute number of 500,000 sperm may be considered a low dose where currently 1 to 10 million sperm are provided. As can be seen, this absolute number is at least 50% or less of any value selected from the current range. For non-livestock animals, the Applicant notes that determining the number of sperm cells in a typical insemination dosage is merely a function of routine experimentation, as discussed below, and therefore is well within the ordinary skill in the art. Accordingly, the Applicant believes the indefiniteness concern has been fully addressed. The Applicant further notes the foregoing comments are equally applicable to the enablement concerns raised in the Office Action with respect to the predictability of low dose insemination.

Regarding the recitation of "success levels comparable to a typical insemination dosage", the Applicant disagrees with the indefiniteness concerns raised. However, to facilitate examination of the current case, the Applicant has cancelled claims 2 and 184 and amended claims 1 and 174-183 to recite "success levels selected from the group consisting of at least 35%, at least 41%, at least 50%, and at least 90% of a typical insemination dosage". As discussed above, the number of sperm cells in a typical insemination dosage is well within the ordinary skill in the art. Accordingly, the Applicant believes the indefiniteness concern has been fully addressed.

Regarding the recitation of "sensing a sex characteristic", the Applicant disagrees with the indefiniteness concerns raised. As stated in the specification at page 9, lines 25-28, sperm cells may be stained to different levels based on the differing length of the X chromosome and the Y chromosome. Thus, by sensing the degree of dye present in the sperm cells it is possible to discriminate between X-bearing sperm and Y-bearing sperm. The specification at page 9, lines 19-23 further states that sensing is accomplished as discussed in U.S. Patent No. 5,135,759. Accordingly, the Applicant believes the recitation of "sensing a sex characteristic" is definite in light of the teaching of the specification.

Regarding the recitation of a "time which is generally regarded as optimal for a single insemination", the Applicant disagrees with the indefiniteness concerns raised. As stated in the specification at page 21, lines 28-30, heifer or cow estrus may be synchronized using known techniques and according to techniques well known in the art. In as much as the art for synchronizing estrus is known, it may be appreciated that an optimal time for insemination is known. The specification at page 22, lines 6-8 implicitly teaches this by stating that artificial insemination "may be accomplished not at the peak moment as typically used in artificial insemination, but rather at a somewhat later moment such as 12 hours after that time since there is some possibility that fertility for sexed artificial insemination may occur slightly later". For non-bovine animals, the Applicant notes that determining an optimal time for insemination is merely a function of routine experimentation, as discussed below, and therefore is well within the ordinary skill in the art. Accordingly, the Applicant believes the indefiniteness concern has been fully addressed.

Regarding the indefiniteness concern raised with respect to claims 16-18, 24-29, and 165-168, the Applicant disagrees with the indefiniteness concern raised. However, in order to facilitate examination of the current case, the Applicant has amended claim 16 to add the clause "wherein said step of separating further comprises the steps of" to further clarify claim 16. Accordingly, the Applicant believes the indefiniteness concern has been fully addressed.

Regarding the indefiniteness concern raised with respect to claim 18, the Applicant disagrees with the indefiniteness concern raised. However, in order to facilitate examination of the current case, the Applicant has cancelled claim 18 and amended claims 25, and 167-168.

Regarding the indefiniteness concern raised with respect to claims 171-173, the Applicant disagrees that the recitation of a "substantial portion" is indefinite. However, in order to expedite examination of the current case, the Applicant has cancelled claim

171 and amended claim 172 to eliminate reference to the term "substantial portion". Accordingly, the Applicant believes the indefiniteness concern has been fully addressed.

Regarding the recitation of "stream matched physical characteristics", the Applicant disagrees with the indefiniteness concerns raised. However, to expedite examination of the current case, the Applicant has amended claim 179 to recite separating nonhuman sperm cells "into a stream". Further, the Applicant notes that the specification on page 10 lines 15-17 teaches that the nozzle of a flow cytometer emits a stream and on page 16, lines 10-11 teaches that a collection container which matches the geometry of the stream may be most optimal. Accordingly, the Applicant believes the indefiniteness concern has been fully addressed.

Although not raised as an issue in the Office Action, the Applicant notes that claim 168 has been cancelled and claim 185 has been added to remedy certain claim numbering issues appurtenant to claim 168.

The Office Action raises a number of enablement concerns. As to each of these, the Applicant disagrees that the pending claims are not enabled by the specification. Moreover, it is believed that the changes made in response to the indefiniteness concerns discussed above may alleviate many of the enablement issues raised in the Office Action. However, as to any concerns which remain, it appears as best that can be determined that the Examiner is struggling with the level of experimentation necessary to apply the various separate details of the present case to any nonhuman mammal.

With respect to this point, the Applicant wishes to emphasize (as pointed out in the Office Action) that the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. MPEP § 2164.01; United States v. Teletronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). How a teaching is set forth, by specific example or broad terminology, is not important. MPEP § 2164.08; In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 370 (CCPA

1971). Claims are not rejected as broader than the enabling disclosure for non-inclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious. MPEP § 2164.08; In re Skriyan, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970). In the present case, the Office Action expressly states that the specification provides one specific example in which a method for producing a nonhuman mammal using a low number of separated sperm while achieving success rates comparable to that obtained with a typical insemination sample. As a result, the claims are in fact enabled for bovines with respect to the specific example provided by the specification. Moreover, the specification teaches the inventive principles which were applied in the specific example to enable a successful result in that case. It is these inventive principles that provide the correlation between the teachings of the specification and the scope of the claims and enable the claims for other non-human species.

As may be appreciated, the scope of enablement must only bear a reasonable correlation to the scope of the claims. MPEP § 2164.08; In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. MPEP 2164.01(b); In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). In the present case, the specific example teaches application of broader inventive principles. For example, the present case realizes the relationship of the sheath fluid to the success achieved in using low dose, separated sperm for artificial insemination:

"While naturally it is possible to adjust either the pre- or post-sort fluids, in one embodiment the invention adjusts the sheath fluid (3) so that it imposes significantly less stress upon the cells than was previously accomplished. In one regard the invention is remarkable in that it removes the total focus from that of operation of the flow cytometer to a focus on handling and removing stress from the cells themselves." Specification at page 12, lines 11-16

* * *

"For the sheath fluid, a substance is selected according to one embodiment of the invention so that it may be chemically coordinated to present minimal changes. Thus, by selecting the appropriate sheath fluid not only in context of flow cytometry parameters,

but rather also in context of the cell parameters themselves, the changes experienced by the cells and the over all result of the sorting can be enhanced. This is shown conceptually in Figure 3. Figure 3 shows some type of chemical factor (such as citrate or other factors) as it may exist throughout the various phases of the process. For instance, the four phases shown might represent the following shown for a flow cytometry separation technique, but not to be so limiting: phase I may represent the existence of the cells within the cell source (1), phase II might show the existence of the cells as they are sorted in the sheath fluid environment, phase III might show the cells as they are collected after sorting and phase IV might show the reconstituted cells in a storage medium after sorting. These four phases as shown for the prior art may experience vastly different chemical factor environments. As shown conceptually, however, in the present invention the cells may experience very little change, most notably the dip or drop experienced between phases I and II may be virtually absent. This is as a result of the selection of the appropriate sheath fluid as mentioned above. Thus, as a result of being subjected to an appropriate sheath fluid, the cells in the present invention may experience a much lower level of stress." Specification at page 13, lines 1-18

Applying these principles to bovines, the specification at page 12, lines 23-25 notes that a citrate constancy metabolic composition may be very important and thus that a 2.9% sodium citrate solution is selected and coordinated for the sheath fluid, as taught by the specification at page 13, lines 26-28. More importantly, once it is realized that coordinating a sheath fluid may contribute to the successful use of low dose, separated sperm for artificial insemination, the particular parameters for specific species can be determined by routine experimentation.

As may be appreciated, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP § 2164.01; In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. MPEP § 2164.06; In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.06; In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). In the present case, the Applicant notes that

considerable amounts of complex experimentation are routine for the field of animal reproduction technology. Attention is directed to the experimentation described in the patents and publications cited by the Applicant in the Information Disclosure Statements of the present case, which illustrate this point. Moreover, as discussed above, the teachings of the present case provide guidance for the direction along which experimentation should proceed with respect to other non-human species. As discussed above, for example, once it is recognized that chemically coordinating a sheath fluid is important, the specific parameters for the sheath fluid may be determined by routine experimentation for any particular species. In fact, as described in the specification at page 12, lines 23-25, the teachings of the specification even provide two kinds of sheath fluids – citrate constancies and hepes buffered constancies – as starting points for experimentation.

The Applicant notes that the Office Action cites *Genentech Inc. v Novo Nordisk*, 42 U.S.P.Q.2d 1001 (Fed. Cir. 1997), for the proposition that it is the specification, not the knowledge of one skilled in that art, that must supply the novel aspects of the invention in order to constitute adequate enablement. As discussed above, the Applicant maintains that the specification of the present case in fact does teach novel aspects – it is the application of these novel aspects to specific non-human species that falls within the realm of routine experimentation. Moreover, this point is clarified by a review of *Genentech* itself. As discussed in *Genentech* at page 1010, the question before the court was whether the specification would have enabled a person having ordinary skill in the art at the time of filing to use cleavable fusion expression to make hGH without undue experimentation. However, as discussed in *Genentech* at page 1010, the specification at issue provided *no detail whatsoever* on how to make hGH using cleavable fusion expression. Nor were reaction conditions for the steps needed to produce hGH provided, and no description of any specific cleavable conjugate protein appeared. Further, as discussed in *Genentech* on page 1014, just prior to the sentence cited in the Office Action, there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill in the art when there is *no disclosure of any specific starting material or of any of the conditions under*

which a process can be carried out. These conditions spelled out in *Genentech* are not the situation in the present case. As discussed above, for example with respect to the importance of chemically coordinating a sheath fluid, the conditions affecting the use of low dose, separated sperm in artificial insemination are described in the specification. Further, starting materials are even provided, as is the case for the citrate constancies and hepes buffered constancies discussed above. Consequently, the application of *Genentech* to the present case is not warranted.

Accordingly, for the reasons discussed above, the Applicant respectfully requests withdrawal of the enablement rejection raised in the Office Action.

The Office Action raises enablement concerns with respect to the values cited in claims 172-173 and 182-183. The Applicant disagrees that these claims are not enabled by the specification. As discussed above, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. MPEP § 2164.01; United States v. Teletronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP § 2164.01; In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Further, a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. MPEP § 2164.03; In re Vickers, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); In re Cook, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. MPEP § 2164.03.

In the present case, as described in the specification on page 8, lines 21-22, the ability to sort sperm is preferably provided through the use of flow cytometry. The use of flow

cytometers to sort various types of cells, including sperm cells, is well known in the art. Indeed, many of the references supplied by the Applicant via Information Disclosure Statement and incorporated by reference in the present case expressly discuss various methods and apparatus related to the use of flow cytometers. As readily may be appreciated, a flow cytometer is a mechanical device having parameters which may be adjusted to direct its performance. It is well known that the accuracy of the sorting percentages achieved by a flow cytometer can be predictably varied by adjusting the parameters of the flow cytometer. As just one example, reducing the sort rate of a flow cytometer predictably increases the accuracy of the sorting percentages achieved by the flow cytometer. In this way, persons skilled in the use of flow cytometers readily may anticipate the effects that changing the parameters of the flow cytometer may have on sorting accuracy. While a degree of experimentation may be required in any given situation to adjust the parameters of the flow cytometer to achieve a desired accuracy of sorting percentages, such experimentation is not atypical in the field of flow cytometry and in any case is facilitated by the predictability of making adjustments to the flow cytometer. For these reasons, the Applicant maintains that the experimentation required to adjust a flow cytometer to achieve a desired accuracy of sorting percentages is not undue. Accordingly, the Applicant submits that claims 172-173 and 182-183 are enabled by the specification.

The Applicant, having addressed each of the concerns raised in the Office Action, respectfully requests reconsideration and withdrawal of the rejections and objections to the application. Allowance of claims 1, 5-12, 16-17, 19-29, 165-167, 169-170, 172-183, and 185 is requested at the Examiner's earliest convenience.

Dated this 20 day of January, 2005.

Respectfully submitted,

SANTANGELO LAW OFFICES, P.C.

By:

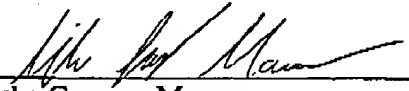

Misha Gregory Macaw
Attorney for Applicant
PTO No. 55,417
125 South Howes, Third Floor
Fort Collins, Colorado 80521
(970) 224-3100

EXHIBIT A